Dopamine and Light: Dissecting the Effects on Mood and Motivational States in Mildly Seasonal Women

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Abstract

Monoamine neurotransmitters are thought to be involved in the pathophysiology of numerous mood disorders, including depression. While the focus during the past few decades has been on serotonin and noradrenaline, there is increasing evidence to suggest that dopamine (DA) may also play a significant role. In particular, one subclassification of depression, Seasonal Affective Disorder (SAD), presents with a symptom profile particularly suggestive of a hypoactive DA system. One of the first-line interventions for the treatment of SAD is bright light therapy. Interestingly, while the mechanism of action underlying the efficacy remains unknown, there is a growing body of evidence that monoamines are sensitive to fluctuations in light exposure and may be directly implicated. To investigate these interactions further we tested whether the mood and motivational effects of lowered DA, as produced by the acute phenylalanine/tyrosine depletion (APTD) method, may be prevented by bright light exposure. Healthy, mildly seasonal women were tested in either bright or dim light conditions. On separate test days they ingested, in a randomized and counterbalanced order, (i) a nutritionally balanced amino acid mixture and, (ii) a mixture deficient in the DA precursors phenylalanine and tyrosine. During each test day mood was assessed at 6 different time points using the Profile of Mood States. Motivation to seek monetary reward was assessed by performance on a progressive ratio breakpoint task. Data analysis yielded two primary findings. First, APTD led to lowered mood and motivational states resembling those seen in patients with SAD. Secondly, bright light exposure prevented the effects on mood but not energy levels or the motivation to work for a reward. These findings suggest that the effects of DA on motivational states are not secondary to lowered mood levels and that acute light exposure might diminish low mood states through non-DA related processes.

Résumé

Les neurotransmetteurs monoamines sont soupçonnés d'être impliqués dans la physiopathologie de nombreux troubles de l'humeur, y compris la dépression. Bien que l'accent a été jusqu'à présent essentiellement sur la sérotonine et la noradrénaline, des éléments de preuve de plus en plus nombreux tendent à suggérer que la dopamine (DA) jouerait également un rôle important. En particulier, une sous-classification de la dépression, le trouble affectif saisonnier (SAD), présente un profil de symptômes particulièrement suggestif d'un système hypoactif DA. L'une des interventions premières pour le traitement de SAD est la luminothérapie. Alors que le mécanisme d'action sous-jacent de l'efficacité de ces traitements reste inconnu, un nombre croissant de preuves suggère que les monoamines sont sensibles aux fluctuations de l'exposition lumineuse et qu'ils pourraient directement être impliqués. Pour étudier ces interactions, nous avons testé l'hypothèse que les effets d'humeur et comportementaux de la baisse de DA produite par la méthode de déplétion aigüe de phénylalanine / tyrosine (APTD), peut être empêchée par exposition à la lumière vive. Des femmes en bonne santé et modérément saisonnières ont été testées dans des conditions de lumière soit vive soit sombre. Au court de journées distinctes et dans un ordre aléatoire et contrebalancé, ces femmes ont ingéré (i) un mélange nutritionnel équilibré en acides aminés et, (ii) un mélange pauvre en phénylalanine et tyrosine; tous deux précurseurs de DA. Tout au long de la journée de test, l'humeur a été évaluée à 5 points de temps différents en utilisant le Profile of Mood States. En outre, leur motivation à poursuivre une récompense monétaire a été évaluée à travers leur performance sur une tâche d'arrêt à ratio progressif. Les résultats ont révélé deux conclusions principales. Tout d'abord, le fait que la baisse de transmission de DA entraîne une baisse de l'humeur et de la motivation ressemblant à celle de patients atteints de SAD. Deuxièmement, l'exposition à la lumière vive a empêché les effets sur l'humeur, mais pas sur le niveau d'énergie ou la motivation de travailler pour une récompense. Ces résultats suggèrent que les effets de DA sur les états de motivation ne sont pas secondaires à des niveaux d'humeur abaissée, et que l'exposition aiguë à la lumière pourrait diminuer la basse humeur liée à la baisse de DA, et ce à travers des processus non reliés à DA.

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Contribution of Authors

McGill University requires that in the case where a multi-author manuscript is included in a thesis an explicit statement of the contribution of the authors is included.

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Elizabeth Cawley (primary author): study execution, data acquisition, analysis and interpretation; drafting of the manuscript and critical revisions.

Sarah Park (co-author): study design, data acquisition and completion of the pilot study of the progressive ratio breakpoint task used in this experiment.

Marije aan het Rot: study design, assistance with data analysis.

Kimberly Sancton: study coordination and data acquisition.

Chawki Benkelfat: study concept and design and medical supervision.

Simon N Young: study concept and design.

Diane Boivin: study concept and design and medical supervision.

Marco Leyton: supervision of primary author and co-author, study concept and design, supervision of data acquisition, interpretation of the data, drafting and critical reviews of the manuscript.

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Introduction

Monoamines

Monoamines, named because they contain one amine group, are synthesized from a single amino acid (AA). They include the three catecholamines, dopamine (DA), noradrenaline (NA), and adrenaline (A), and the indolealkylamine, serotonin (5-HT). Whereas 5-HT innervates all major areas of the brain, catecholamines project primarily to motor, limbic and cognitive areas. Midbrain DA neurons project to three areas in particular: (i) dorsal striatum strongly associated with the initiation of motor activity, (ii) ventral striatum involved in motivation, reinforcement and learning, and (iii) the prefrontal cortex associated with working memory (S. D. Iversen & L. L. Iversen, 2007). These effects of DA have made it a prime target for research into psychiatric disorders such as depression, addiction, and attention deficit hyperactivity disorder (ADHD).

Synthesis and Biochemistry

Monoamine Synthesis

Catecholamines are formed from the amino acid tyrosine. In mammals, tyrosine can be extracted from ingested proteins or synthesized from the essential amino acid, phenylalanine, which is converted to tyrosine by the enzyme phenylalanine hydroxylase, found primarily in the liver (Kaufman, 1957). Blaschko (1939) first proposed the pathway for the biosynthesis of catecholamines. While Blaschko's pathway is still accepted as the major pathway of biosynthesis, because many of the enzymes involved lack specificity alternative pathways also exist (Molinoff & Axelrod, 1971).

Dopamine

The synthesis of tyrosine to DA occurs in both the cytosol and presynaptic terminal of catecholaminergic neurons in a two-step process. The first step is the hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase adding a hydroxyl group to the meta position of tyrosine. Tyrosine hydroxylase can also hydroxylate phenylalanine to form tyrosine, which can then be converted to L-DOPA. Step two involves the rapid decarboxylation of the intermediary L-DOPA by L-amino acid decarboxylase (Holtz, Credner, & Koepp, 1942). The rate-limiting step in the synthesis of DA is the initial step. Because the enzyme L-amino acid decarboxylase has an activity level of 100 to 1000 times that of tyrosine hydroxylase and is abundant in the cytoplasm of catecholaminergic neurons, the production of DA is dependent on the synthesis of tyrosine to L-DOPA (Nagatsu & Levitt, 1964).

Noradrenaline and Adrenaline

DA can be further synthesized to NA and A. In noradrenergic neurons, DA is sequestered into secretory granules that contain the enzyme dopamine-ß-hydroxylase, which subsequently hydroxylates DA to produce NA (Kaufman & Friedman, 1965). In a smaller number of cells that produce A, NA is methylated by the enzyme phenylethanolamine-N-methyltransferase to produce A when the former diffuses out of secretory granules into the cytosol (Kaufman & Friedman, 1965).

Serotonin

Comparably to DA synthesis, which can be affected by the relative availability of its precursor

tyrosine, serotonin (5-hydroxytryptamine, 5-HT) is also sensitive to the supply of its amino acid precursor, tryptophan (Fernstrom, 1983). 5-HT in the brain is synthesized from the essential amino acid tryptophan in a two step-process. In serotonergic neurons, tryptophan is hydroxylated to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase (Lovenberg, Jequier, & Sjoerdsma, 1967). Similarly to DA, this hydroxylation step of 5-HT synthesis is the rate-limiting step. The final step in the synthesis of 5-HT is the decarboxylation of 5-hydroxytryptophan by L-amino acid decarboxylase (Lovenberg, Weissbach, & Udenfriend, 1962), the enzyme that also decarboxylates L-DOPA to produce DA.

Monoamine Metabolism

Dopamine

The action of DA in the synaptic cleft is terminated predominantly by reuptake into the axon terminal by Na+-dependent transporters that pump extracellular DA back into the nerve terminal (Axelrod & Weinshilboum, 1972). Once in the terminal, the molecules are recycled back into synaptic vesicles for reuse, or degraded by the enzyme monoamine oxidase (MAO). In the frontal lobes, reuptake of DA occurs via NA transporters to NA terminals (Molinoff & Axelrod, 1971).

Extracellularly, DA can be inactivated via two metabolic pathways. DA can be deaminated by both forms of MAO (MAO-A and MAO-B) to form 3,4-dihydroxy-phenylacetaldehyde (DOPAL). This intermediate, DOPAL, is further metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC). Homovanillic acid (HVA), the major end product of DA metabolism, can then be formed by *O*-methylation of DOPAC by catechol-*O*-methyltransferase (COMT). The second

degradative pathway begins with the *O*-methylation of DA by COMT to form 3-methoxytyramine. The oxidative deamination of this intermediary by MAO results in HVA (Molinoff & Axelrod, 1971).

Serotonin

The action of 5-HT can also be terminated by two major pathways, reuptake into the nerve and inactivation by MAO. Unlike catecholamines, 5-HT cannot be metabolized by *O*-methylation by COMT because of differences in composition and structures

The action of 5-HT in the synaptic cleft is terminated predominantly by reuptake. When 5-HT has been released, it can bind to postsynaptic 5-HT receptors or 5-HT autoreceptors on the presynaptic membrane. Here, the highly selective serotonin transporter (SERT) is responsible for removing 5-HT and transporting it into the presynpatic neuron where 5-HT is recycled back into presynaptic vesicles and it is protected from metabolism (Ni & Watts, 2006).

The second method of metabolism by MAO occurs within the cytosol of the neuron. 5-HT is first deaminated by MAO-A. The product of this oxidative deamination is the aldehyde, 5-hydroxyindoleacetaldehyde, which can then either be oxidized by aldehyde hydrogenase to 5-hydroxyindoleacetic acid (5HIAA), or reduced to 5-hydroxytryptophol by an aldehyde reductase (Mohammad-Zadeh, Moses, & Gwaltney-Brant, 2008; Tyce, 1990).

Monoamines and Depression

It is proposed that changes in mood and behavior are linked to brain monoamines, NA, A, DA and 5-HT. An early theory of depression was termed the "amine hypothesis of affective disorders" and it postulated that depression was associated with an absolute or relative deficiency of NA and/or 5-HT at functionally important receptor sites in the brain (Schildkraut, 1965). This hypothesis has been supported by literature demonstrating that decreases in 5-HT and/or NA can result in a lowering of mood (Ellenbogen, Young, Dean, Palmour, & Benkelfat, 1996; aan het Rot, Moskowitz, & Young, 2008), reinstate depressive symptoms in remitted patients (Berman et al., 2002; Hasler et al., 2008; Smith, Fairburn, & Cowen, 1997; Neumeister et al., 1998), and reverse the efficacious effects of serotonergic (Delgado et al., 1990) and noradrenergic antidepressants (Miller et al., 1996).

While research into the biological underpinnings of mood disorders has, until recently, been focused largely on NA and 5-HT, accumulating evidence suggests that changes in NA and 5-HT do not account for all of the psychotropic effects observed. Although selective serotonin reuptake inhibitors (SSRI) have become the first-line treatment for many depressive disorders, a large proportion of patients (28-55%) fail to fully recover, or experience residual symptoms (Nierenberg & DeCecco, 2001; Nierenberg & Wright, 1999). Secondly, symptoms associated with depressive disorders such as lethargy, psychomotor retardation and low motivation are suggestive of a hypoactive DA system. One theory of depression implicating three monoamine systems (5-HT, DA, and NA) has postulated that there are two clusters of depression-related symptoms, (i) increased negative affect (*e.g.,* fear, anxiety, and irritability), and (ii) decreased positive affect (*e.g.,* decreased pleasure, loss of interest, fatigue, and/or loss of energy; Nutt et al.,

2007). Moreover, these two clusters would be differentially affected by different neurotransmitter systems, the development of negative affect being primarily serotonergic and a decrease of positive affect being predominantly dopaminergic. Finally, both systems could also be affected by NA (Nutt et al., 2007).

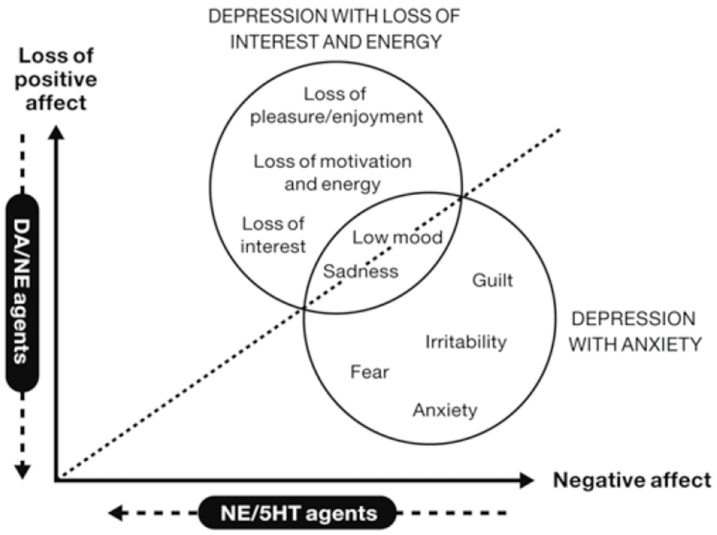

Figure 1: Hypothetical model showing different actions of antidepressant agents on symptoms of positive and negative affect (From Nutt et al., 2007 and reprinted with permission from Sage Publications).

While it is certainly advantageous to explore theories of depression involving more monoamine systems and their interactions, it is likely that a theory of depression limited to a decreased activity in monoamine system(s) is overly simplified. It is uncertain if hypoactive monoamine systems are a cause or (possibly aggravating) by-product of depression, and to date a direct causal relationship has yet to be made. It is possible that monoamine systems are important in characterizing a vulnerability to depression. Three systematic reviews of the literature have independently shown that monoamine depletions alone do not cause a mood lowering effect in healthy individuals, yet, monoamine depletions in vulnerable populations (*e.g.,* recovered depressed patients or individuals with a family history of depression) have more consistently

shown mood lowering effects (Booij, Van der Does, & Riedel, 2003; Fusar-Poli et al., 2006; Ruhé, Mason, & Schene, 2007).

Antidepressants

In the l950s the first two types of antidepressants were discovered serendipitously (for a review, see Papakostas, 2006). The first, iproniazid, was originally prescribed for the treatment of tuberculosis; however it was noted that some patients developed euphoria and hyperactive behavior (Crane, 1956). Following this, imipramine, which was developed as an antihistamine, was noted to have striking antidepressant effects in patients with endogenous depression relieving, in particular, symptoms of low energy and psychomotor retardation (Kuhn, 1958). Subsequent work indicated that iproniazid was a potent monoamine oxidase inhibitor (MAOI) that increases brain concentrations of 5-HT and NA (Loomer, Saunders, & Kline, 1957; Spector, Shore, & Brodie, 1960), while imipramine blocks 5-HT and NA transporters (Carlsson, Corrodi, Fuxe, & Hökfelt, 1969; Glowinski & Axelrod, 1964). Since then, variations of these compounds have resulted in a large number of antidepressants that target primarily NA, 5-HT, or both (Montgomery, Stokes, Kitamura, & Grasby, 2007). Interestingly, however, there is some evidence that while not primarily targeted, some of the therapeutic effects of these older antidepressants could also reflect additional changes in the DA system (Judd et al., 1998; Petersen et al., 2005).

Dopamine and Mood

There is some research to support the theory of a dysfunctional DA system contributing to depression in some patients. Significant decreases of CSF HVA levels and/or plasma DA have

been shown in depressed patients, most consistently in those with psychomotor retardation (Tandon, Channabasavanna, & Greden, 1988). In manic patients, either normal or increased levels of DA metabolites have been observed (Klimek, Schenck, Han, Stockmeier, & Ordway, 2002). From these observations it has been hypothesized that monoamine metabolites could be used as a biochemical classification for affective disorders. One study in particular measured CSF HVA and 5-HIAA (a 5-HT metabolite) levels in manic and depressed patients and reported that these metabolites corresponded to clinical symptomatology and could be used to correctly classify patients as manic or depressed (Shah, Ogilvie, Goodwin, & Ebmeier, 1997).

More recently, neuroimaging and histopathological studies have also shown greater post-mortem D_2 receptor binding and decreased DA transporter (DAT) binding potential in the amygdala of depressed patients (Meyer, Krüger, & Wilson, 2001), decreased D_2/D_3 receptor binding in the striatum (Hirvonen et al., 2008; Parsey et al., 2001) and decreased DAT binding in the striatum compared to controls (Delgado et al., 1993; Delgado, Moreno, Onate, & Gelenberg, 2002; Miller et al., 1996). Moreover, one study showed that while a group of depressed patients all exhibited increased striatal D_2 receptor binding potential (possibly indicating decreased extracellular DA levels), the increased binding was most significant in those patients that exhibited psychomotor retardation (Berman et al., 1999; see also Meyer et al., 2006). However, it should be noted that these findings are not conclusive and some studies showing no differences in DA receptor or transporter availability have also been reported (Neumeister et al., 1998).

Effects of Dopamine Manipulations

Three main methods have been used to lower DA function in humans, alpha-methylparatyrosine (AMPT), DA receptor antagonists, and acute phenylalanine tyrosine depletion (APTD), with the research stemming from these three methods providing heterogeneous results. To date, there have been two comprehensive reviews of monoamine depletion studies (including AMPT and APTD) by Booij et al., 2003 and Ruhé et al., 2007.

Alpha-methylparatyrosine

Alpha-methylparatyrosine temporarily reduces L-DOPA availability by blocking the enzyme tyrosine hydroxylase, which subsequently reduces catecholamine synthesis.

AMPT has been shown to reinstate depressive symptoms in remitted depressed patients who had been treated with NA reuptake inhibitors, or mirtazapine (a tricyclic antidepressant targeting NA and 5-HT; McCann et al., 1995). In three studies, administration of AMPT induced a transient depressed mood in patients who had been successfully treated with NA-targeted antidepressants but not in those who had been successfully treated with an SSRI. Remittance of depressive symptoms following AMPT has also been seen in medication-free remitted patients (remission > 4 months; Booij, Van der Does, & Riedel, 2003), and individuals with seasonal affective disorder successfully treated with light therapy (Neumeister et al., 1998).

In healthy volunteers AMPT does not generally induce depressive symptoms but has been shown to slightly lower mood in some individuals. More consistent are the sedative effects of AMPT (sleepiness, fatigue, and decreased alertness) and administration of L-DOPA has been shown to reverse these effects (McCann et al., 1995).

AMPT has also been shown to have effects on cognitive function and these seem to be mediated by dopaminergic function (Booij et al., 2003). In healthy volunteers AMPT impaired attention and these effects were associated with lowered DA function as measured by increased [^{11}C]raclopride binding. Another study reported decreased performance on memory and attention tasks when combined with a 40-hour sleep deprivation (McCann et al., 1992).

While AMPT has been used in many experimental studies, it is believed to be less specific than the amino acid depletion method as it potently affects both DA and NA. In addition, AMPT is more time consuming than other methods as it requires multiple daily treatments, and it can cause marked sedation that may mask other effects. AMPT can also induce crystalluria (Brogden, Heel, Speight, & Avery, 1981) and acute dystonic reactions (McCann, Penetar, & Belenky, 1990). The more marked effects of AMPT versus APTD can be an advantage or a disadvantage, depending on the question being asked. For questions about DA's role in cognitive processes and mood and motivational states, APTD has become the more frequently used method.

Acute Phenylalanine Tyrosine Depletion

In humans, transiently decreasing catecholamine transmission with APTD has not been shown to induce significant mood lowering in healthy individuals or to reinstate depressive symptoms in individuals recovered from a history of major depression (Booij et al., 2003; McTavish, Mannie, Harmer, & Cowen, 2005). However, mild mood lowering effects have been seen in healthy individuals following a psychological stressor, such as public speaking (Leyton et al., 2000). APTD has also decreased subjective reports of feeling good (Linssen, Riedel, & Sambeth, 2011) and induced small increases in reported anger, tension and boredom, however these findings have

not been consistent (Grevet et al., 2002; Harmer, McTavish, Clark, Goodwin, & Cowen, 2001; Leyton et al., 2000). More consistent has been the ability of APTD to disrupt preferential and sustained responding for reward-paired cues (Leyton et al., 2007) and successive units of abused substances (Barrett et al., 2008; Venugopalan et al., 2011).

Dopamine Agonists and Antagonists

In humans, medications with DA augmenting effects have been shown to have antidepressant efficacy, particularly in patients with low pre-treatment CSF HVA (Corrigan, Denahan, Wright, Ragual, & Evans, 2000; Post et al., 1978). One study tested the effectiveness of three different antidepressant types in patients with retarded depression (exhibiting features such as hypokinesia, anergia, reduction of speech, hypersomnia, slowness, and drowsiness; Rampello, Nicoletti, & Raffaele, 1991). In this study, patients exhibiting combinations of retarded symptoms were administered amineptine (a DA uptake inhibitor), clomipramine (SSRI) or minaprine (which increases both DA and 5-HT transmission). Amineptine and minaprine were found to be more therapeutically effective than either clomipramine or placebo, with the degree of effectiveness paralleling the specificity of the antidepressant to its pro-dopaminergic effects (Rampello, Nicoletti, & Raffaele, 1991). Amineptine is a tricyclic antidepressant-derivative that predominantly inhibits dopaminergic reuptake with almost no NA or 5-HT activity (Ceci, Garattini, Gobbi, & Mennini, 1986). Amineptine has been shown to have antidepressant properties (Boyer & Lecrubier, 1996) with clinical efficacy similar to MAOs (Macher & Mirabaud, 1992), SSRIs (Dalery, 1997), and tricyclic antidepressants (Van Amerongen, 1979; Bornstein, 1979; Lemoine et al., 1981; Mendis, 1989; Rampello, 1995; Vauterin & Bazot, 1979). However, due to reports of abuse this drug it is no longer available in North America. More

common is the practice of augmenting traditional antidepressants with pro-dopaminergic agents such as pramipexole or psychostimulants (amphetamine or methylphenidate, which alone increase euphoria and positive affect). One study showed effective adjunct therapy with methylphenidate and citalopram in elderly patients (Lavretsky & Kumar, 2001) and there is some evidence from small, open-label studies for the effective augmentation of tricyclic antidepressants and SSRIs with pramipexole (Cassano, 2004; DeBattista, 2000).

Dopamine and Reward

One of the most widely studied effects of limbic DA transmission is the transmitter's influence on approach toward reward and reward related stimuli. In the laboratory, exposure to natural and pharmacological rewards increase limbic DA release (Di Chiara & Imperato, 1988; Hernandez & Hoebel, 1988); treatments that selectively increase DA transmission enhance the pursuit of rewards (Rothman & Glowa, 1995; Woolverton, Goldberg, & Ginos, 1984; Wyvell & Berridge, 2000); and treatments that decrease DA transmission disrupt reward seeking behaviors (Wise, Spindler, & Legault, 1978; De Wit & Wise, 1977; Yokel & Wise, 1975). One early interpretation of these effects proposed that DA mediated the pleasurable aspects commonly associated with reward (Wise, 1982) and studies in humans have provided some support for this proposal. As in laboratory animals, both natural (Small, Jones-Gotman, & Dagher, 2003) and pharmacological rewards (Boileau et al., 2006; Cox et al., 2009; Leyton, 2002) increase striatal DA release. Moreover, in the majority of neuroimaging studies, individual differences in the magnitude of DA response correlated with positive affective states and pleasure (Barrett, Boileau, Okker, Pihl, & Dagher, 2004; Boileau et al., 2006, 2007; Drevets et al., 2001; Laruelle et al., 1995; Martinez et al., 2003; Volkow et al., 1999)

Accumulating evidence, though, does not support the proposal that DA mediates pleasure. For example, administration of the selective and direct DA agonist apomorphine[1] does not cause euphoria (Hollander, Nunes, DeCaria, & Quitkin, 1990; Wiesbeck, Mauerer, Thome, Jakob, & Boening, 1995), and treatments that decrease DA transmission do not consistently diminish the pleasurable effects of rewarding drugs (Leyton, 2009). Moreover, striatal DA release can also be induced by events that are not necessarily pleasurable. Two independent imaging studies have shown increased striatal DA release associated with an aversive stressful math task (Pruessner, Champagne, Meaney, & Dagher, 2004; Volkow et al., 2004). In one task, methylphenidate increased extracellular DA release in the striatum, but only when subjects also performed a stress-inducing math task and not when given placebo or when given methylphenidate plus a neutral task. In parallel to the observed increase of extracellular DA release, subjects also reported greater interest and motivation following methylphenidate and the stressful task compared to the other conditions (Volkow et al., 2004). It was postulated that administration of methylphenidate increased the saliency of the math task to a degree that the methylphenidate/math task condition produced marked increases in DA release whereas the math task alone was not salient enough to produce this effect (Volkow et al., 2004). This finding was replicated using a goal-directed motor task, a video game in which subjects had to navigate a tank through a maze and collect flags. Again, it was shown that there was a significant increase in ventral striatum DA release when playing the game, and there was a significant correlation between performance level achieved and the DA response (M. J. Koepp et al., 1998). Subsequent studies also provide support for DA's role in the incentive salience of reward-paired stimuli, i.e.

[1] Apomorphine is often considered a selective and direct DA agonist although it also has a high affinity for some adrenergic receptors (Millan et al., 2002).

the ability of rewarding objects to sustain interest or elicit motivation, independent of the pleasurable aspects (Berridge, 2007; Leyton et al., 2007; Roiser et al., 2005). For example, in a study by Leyton et al. (2007) 14 healthy men were given *d*-amphetamine and the effects of APTD, APTD+L-DOPA, and a control mixture were tested. APTD selectively increased commission errors for reward-paired cues on a Go/No-Go task, but had no effect on stimuli unpaired with reward. Moreover, the administration of L-DOPA immediately following APTD prevented the effects of APTD and reinstated performance to a level not significantly different from the control condition. Interestingly, while APTD affected the disposition to respond preferentially to reward-paired cues, it did not alter the mood-elevating effect of *d*-amphetamine.

Similarly, in a study of 47 smokers varying across three levels of tobacco use (early low-frequency smokers, stable low-frequency smokers and stable high-frequency smokers) APTD has been shown to decrease motivation to self-administer mini-nicotine containing cigarettes, as measured on a progressive ratio (PR) breakpoint task. These APTD-induced reductions in PR breakpoints occurred in the absence of changes to conscious craving or pleasure (Venugopalan et al., 2011). The ability of APTD to reduce self-administration of rewards both in free-choice paradigms (Leyton et al., 2000) and on a PR task (Barrett et al., 2008) has been shown in similar studies.

In summary, growing evidence suggests that DA neurotransmission affects the ability of appetitive stimuli to elicit or sustain attention and/or motivation for rewarding stimuli, and this behavioral modification can occur in the absence of changes to subjective hedonic experience of the reward.

APTD Method

Acute phenylalanine tyrosine depletion (APTD) is a dietary method designed to transiently lower brain DA synthesis. APTD is based on the principles of a similar method, acute tryptophan depletion (ATD), that was developed by Young et al. (1985) over two decades ago and has since been widely adopted as an experimental method for studying the role of 5-HT synthesis on numerous physical and behavioral processes in humans.

In APTD studies, participants ingest a mixture of essential amino acids that is deficient in the catecholamine precursors phenylalanine and tyrosine. The formulation of the mixture was based on the original balanced (100g) ATD mixture used by Young et al. (1985). The mixture was subsequently adapted for the lower body weight of women (～16.7% less than men) by reducing the mixture to 85.5g (Ellenbogen et al., 1996). The amino acids are given in the same proportion that they occur in human milk, with the exception of glutamate and aspartate, which are excluded due to concerns about their toxicity. The exclusion of these amino acids does not affect the ability of the APTD mixture to lower plasma and brain phenylalanine and tyrosine availability because glutamate and aspartate are non-essential amino acids (Young et al., 1985). The APTD mixture contained 14 AAs: l-alanine 4.6g; l-arginine 4.1g; l-cysteine 2.3g; glycine 2.7g; l-histidine 2.7g; l-isolucine 6.7g; l-leucine 11.3g; l-lysine monohydrochloride 9.2g; l-methionine 2.5g; l-proline 10.2g; l-serine 5.8g; l-threonine 5.4g; l-tryptophan 1.9g; l-valine 7.4g. The control mixture is identical to the experimental mixture with the addition of l-phenylalanine 4.8g and l-tyrosine 5.8g.

In an attempt to minimize the unpalatable taste of the mixture, l-lysine was substituted for l-

lysine monohydrochloride (Young et al., 1985). In addition, due to the offensive odor and taste of the amino acids l-arginine, l-cysteine, and l- methionine, they were encapsulated in 0.95 ml gelatin capsules and administered separately from the amino acid mixture.

Prior to administration of the mixture, participants are asked to consume a low protein diet and fast from midnight the evening before. While no direct studies have verified the necessity of the diet and fasting, one study did note lower than average tyrosine and phenylalanine depletion effects when participants did not fast (Sheehan, Tharyan, McTavish, Campling, & Cowen, 1996). Administration of the amino acid mixtures stimulates protein synthesis. Given the absence of tyrosine and phenylalanine from the APTD mixture these AAs are taken from plasma stores for the incorporation into proteins, which will lower the relative availability of these amino acids in plasma and reduce uptake into the brain.

Since the rate-limiting enzyme in catecholamine synthesis, tyrosine hydroxylase, is usually incompletely saturated with tyrosine, reducing tyrosine availability reduces catecholamine synthesis (Carlsson & Lindqvist, 1978) and DA release (Leyton et al., 2004; McTavish, Cowen, & Sharp, 1999; Montgomery, McTavish, Cowen, & Grasby, 2003). Maximal depletion occurs approximately 5-7 hours after ingestion of the AA mixture (Booij et al., 2003).

APTD Dopamine Specificity

A methodological concern of APTD is the selectivity for DA. While initially it was thought that APTD decreased DA and NA given they are synthesized in the same cascade (DA can be synthesized to NA by dopamine-β-hydroxylase), accumulating evidence suggests that it primarily

affects DA (McTavish, Cowen, et al., 1999). For example, an animal study on brain catecholamine synthesis and release showed that administration of a tyrosine/phenylalanine-free amino acid mixture decreased regional brain tyrosine levels by 50-60% within two hours of administration, which then resulted in decreased DOPA accumulation (following administration of a dopamine-β-hydroxylase inhibitor NSD 1015). Most notably, the decrease in DOPA accumulation was greatest in areas with predominantly dopaminergic innervations (nucleus accumbens and striatum) and less so in areas with predominantly noradrenergic innervations (cortex, hypothalamus, and hippocampus; McTavish, Cowen, et al., 1999). In a second part of that experiment, amphetamine-induced DA release was reduced in a dose-dependent manner following administration of the tyrosine-free amino acid mixture, but showed no effect on amphetamine induced NA release. Finally, administration of a tyrosine-containing load largely restored the amphetamine-induced DA response, albeit not to the level of the saline control (See Figure 2: McTavish, Cowen, et al., 1999).

A subsequent study by this group replicated the finding that administration of a tyrosine/phenylalanine-free mixture had no effect on baseline extracellular NA levels, and moreover did not alter the NA release caused by administration of the α_2-adrenoreceptor antagonist, idazoxan. In comparison, administration of AMPT caused a marked decrease in extracellular NA and abolished the idazoxan-induced increase in NA (McTavish, Callado, Cowen, & Sharp, 1999). The marked difference in effects between AMPT and the tyrosine-free mixture certainly suggest that AMPT is affecting both DA and NA systems, while the tyrosine-free mixture seems to selectively alter DA levels.

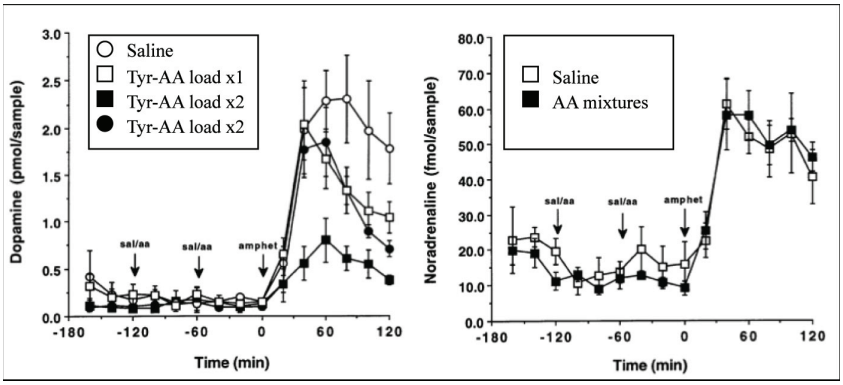

Figure 2: Effect of tyrosine-free, tyrosine supplemented amino acid mixtures, and saline on both basal and amphetamine evoked DA release in rat striatum (from McTavish, Cowen, et al., 1999 and reprinted with permission from Springer).

Preferential effects on DA have also been seen in studies conducted in humans. In imaging studies, APTD has been shown to decrease extracellular DA levels as indicated by increase striatal [^{11}C]raclopride binding (Leyton et al., 2004; Montgomery et al., 2003) and circulating prolactin levels (indicative of reduced DA function; Harmer et al., 2001), but had no effect on plasma melatonin, a neuroendocrine index of noradrenergic neurotransmission (Sheehan et al., 1996).

Seasonal Affective Disorder

The influence of seasonal changes on psychiatric disorders has been recognized since classical times (Wehr & Rosenthal, 1989). However, it was not until the seminal paper by Rosenthal et al. (1984) that seasonal affective disorder (SAD), was formally described. Shortly after, SAD was incorporated into the Diagnostic and Statistical Manual-III-R (DSM-III-R), not as a distinct disorder but as a "specifier" which could be applied to recurrent forms of mood disorders (bipolar disorder, recurrent major depression and both bipolar and major depression not otherwise

specified). The criteria for a seasonal specifier has since been revised for the DSM-IV in which a seasonal pattern can only be applied to recurrent forms of bipolar I, bipolar II or major depressive disorder (American Psychiatric Association, 2000). The defining criterion of SAD is the regular temporal relationship between major depressive episodes (MDE) and a particular time of year. In most cases, the onset of depressive symptoms occurs in the fall with full remission in spring. The opposite pattern of seasonal disturbance (onset in spring or summer with remission in fall) has also been known to occur but has been observed far less frequently, with prevalence rates of up to 3% in the general population (Boyce & Parker, 1988; Rosen et al., 1990; Wehr & Sack, 1987).

In addition to having recurrent MDEs, a diagnosis of SAD requires that the seasonal depressive episodes have occurred for a minimum of two years without any "non-seasonal" episodes during that time. In addition, over a patient's lifetime the number of seasonal MDEs must significantly outweigh the number of non-seasonal MDEs experienced.

Symptom Profile

Individuals with SAD have a characteristic symptom profile that is distinct from other clinical groups, including other depressive disorders. MDEs that occur in a seasonal pattern are often characterized by so-called reverse vegetative symptoms of depression such as hypersomnia, hyperphagia, and weight gain as well as prominent anergy and a craving for carbohydrates (American Psychiatric Association, 2000; Garvey, Wesner, & Godes, 1988; Rosenthal et al., 1984).

Rosenthal's initial paper (1984) described 29 patients with winter depression, all of whom reported sadness and decreased physical activity during their winter depressed periods. In addition, 66% experienced hyperphagia, 79% had carbohydrate cravings, 76% had weight gain (usually 2-5kg), and 97% reported hypersomnia. Since this first description of patients with winter depression this symptom profile has been consistently observed in patients with SAD.

Prevalence

The estimate of prevalence for depression with a seasonal pattern has been variable. An overview of epidemiological studies showed prevalence rates from community surveys ranging from 0.0% to 9.7% (Magnusson, 2000), and between 10% and 20% in patient populations (Faedda et al., 1993). However, The National Comorbidity Survey (NCS) reported rates of major depression with a seasonal pattern, and minor depression with a seasonal pattern at 0.4% and 1.0%, respectively (Blazer, Kessler, & Swartz, 1998). The difference in prevalence rates is attributable to the diagnostic criteria used. In most prevalence studies of SAD Rosenthal's Seasonal Pattern Assessment Questionnaire is used, which assesses the severity of seasonal mood disturbances without the actual prevalence of MDEs. When the stricter DSM-III-R criteria are applied, as they were in the NCS, then prevalence rates of SAD are drastically reduced (see Table 1).

Comparison of diagnostic criteria for SAD/seasonal pattern

Rosenthal criteria for winter depression	DSM-III-R criteria for seasonal pattern modifier	DSM-IV criteria for seasonal pattern specifier	ICD-1O criteria for seasonal depressive disorder
Recurrent fall/ winter depressions	Regular onset within a 60-day period	Regular temporal relationship with a particular time of year	Regular onset of episodes within specific 90-day period
No seasonally varying psychosocial stressor	Excludes seasonal psychosocial stressors	Excludes seasonal psychosocial stressors	
Regularly occurring non-depressed periods in spring and summer	Full remission or switch to (hypo)mania within 60-day period	Full remission or switch to (hypo)mania at characteristic time of year	Remission within particular 90-day period
At least two of the depressions occurred during consecutive years	At least three episodes, two in consecutive years; ratio of 3:1 seasonal:nonseasonal episodes	Seasonal major depressive episodes occurred, and non-seasonal MDEs* did not occur, for the past two years; lifetime seasonal MDEs outnumber non-seasonal MDEs	Three or more consecutive episodes; seasonal episodes substantially outnumber any nonseasonal episodes
At least one of the depressions has met RDC** for major depression	May apply to bipolar disorders, recurrent major depression, depressive disorder not other-wise specified	Applies to bipolar disorder (type I or II) or major depressive disorder, recurrent	Applies to ICD-10 major depression
No other axis I pathology	Other diagnoses do not exclude application of the modifier	Other diagnoses do not exclude application of the specifier	Other mental and behavioural disorders do not exclude the diagnosis

*MDEs = major depressive episodes.
**RDC = research diagnostic criteria.

Table 1: Comparison of diagnostic criteria for seasonal affective disorder (from Lam & Levitt, 1999 and reprinted with permission from the editor).

SAD has also shown increased prevalence rates in women and young people (under 25 years), and there is a trend towards increased prevalence rates with increasing latitude, although the latter finding is controversial. In a review of the literature Mersch et al. (1999) found a small correlation between latitude and the prevalence rates of SAD (North America: $r = 0.90$, $p = 0.003$ and Europe: $r = 0.70$, $p=0.061$). However, the authors suggest that other factors such as climate, genetics, and social-cultural context play a greater role in the variance contributing to differential prevalence rates.

Subsyndromal Seasonal Affective Disorder

A milder form of SAD, termed subsyndromal-SAD (S-SAD), has been identified also. The DSM-IV-TR outlines that the seasonal specifier applies only to the seasonal occurrence of full MDEs

but it is acknowledge that a seasonal pattern may also describe the presentation of seasonal depression in individuals who do not meet criteria for a MDE. It has been postulated that "seasonality" can be thought of as along a continuum, with seasonal DSM-defined SAD at one extreme and normal, non-symptomatic individuals at the other. Along this continuum there appears to be an additional group of individuals that do not meet full criteria for SAD but are affected by seasonal variations in mood, energy, sleep and behavior who have been referred to as having S-SAD. Kasper et al. (1989) observed that individuals with S-SAD had a similar experience to patients with SAD who experience an onset of symptoms in October, a peak in symptomatology around January and February, and remittance in March; these months have also been highlighted by control subjects as months where they "felt the worst" but did not indicated that the changes experienced were problematic, as is found in S-SAD and SAD patients.

Reported prevalence rates of S-SAD are also highly variable, with rates ranging from 1.7% to 14.8% depending on location and the diagnostic criteria used (Booker & Hellekson, 1992; Kasper, Wehr, Bartko, Gaist, & Rosenthal, 1989; Mersch et al., 1999; Rosen et al., 1990)

Pathophysiology of Seasonal Affective Disorder

While DA has been hypothesized to play a role in depression, as noted previously, the symptom profile seen in SAD consisting largely of lethargy, psychomotor retardation, weight gain, and low motivation, are highly suggestive of a hypoactive DA system and the human literature does offer support for this. First, decreasing DA synthesis via APTD in remitted SAD patients has been shown to induce an acute relapse of depressive symptoms (Neumeister, Turner, et al., 1998). As well, neuroimaging studies of SAD patients have shown decreased availability of striatal DA

transporter binding sites, in addition to lower serum prolactin levels (Depue, Arbisi, & Spoont, 1989; Depue et al., 1990; Oren, Levendosky, Kasper, C. C. Duncan, & Rosenthal, 1996) and reduced eye-blink rates (Barbato, Moul, Schwartz, & Rosenthal, 1993; Depue et al., 1989), both of which are markers of reduced DA levels. Similar to the dyadic subgroup theory of depression proposed by Nutt et al. (2007), Levitan (2007) has suggested that DA and 5-HT play distinct roles in the symptomatology of SAD, with DA playing a unique role in the appetitive symptoms, which are distinct from the affective symptoms putatively more attributable to 5-HT.

Light Therapy

Coincident with the first description of winter depression by Rosenthal et al. (1984) was evidence that bright artificial light had an antidepressant effect. A meta-analysis of the efficacy of light therapy commissioned by the American Psychiatric Association and conducted by Golden et al. (2005) found that light therapy and dawn simulation for SAD, and light therapy for non-seasonal depression were efficacious treatments (effect size 0.84, 0.73 and 0.53, respectively), with effect sizes similar to those seen in randomized-controlled trials for pharmacological antidepressants (Golden et al., 2005). Multiple reviews of light therapy as a treatment for SAD have concluded that fluorescent light boxes are an effective treatment and The Canadian Consensus Guidelines for the Treatment of SAD have outlined that bright light therapy, using a fluorescent light box with light intensities greater than 2,500 lux, is an effective first-line treatment, with approximately 65% of patients having a good clinical response (Lam & A. J. Levitt, 1999; Lam, M. Terman, & Wirz-Justice, 1997).

Interestingly, the beneficial effects of light therapy have also been reported in other clinical populations including antepartum depression (Wirz-Justice et al., 2011), non-seasonal major depressive disorder (Lieverse et al., 2011), and eating disorders (Janas-Kozik et al., 2011). In particular, light therapy may be especially effective in those patients who experience a seasonal exacerbation of their symptoms (Lam, Goldner, Solyom, & Remick, 1994).

Light and Dopamine

Despite the now consistent evidence of light's antidepressant effect (Golden et al., 2005), the mechanisms of action remain poorly understood. However, a number of candidates have been implicated as it has been shown that light exposure can affect 5-HT (Héry, Rouer, & Glowinski, 1972), melatonin (Lewy, Wehr, F. K. Goodwin, Newsome, & Markey, 1980; Oren, 1991)(Lewy et al., 1980; Oren, 1991), catecholamines (Nagayama, 1999), and cortisol (Jung et al., 2010).

Given the extensive literature on its role in depression, 5-HT was identified early on as a likely mechanism implicated in light therapy. Since then, it has been demonstrated that decreasing 5-HT synthesis with ATD can reinstate depressive symptoms in SAD patients during summer remission (Leyton et al., 2000; Neumeister, Turner, et al., 1998), and those successfully treated with phototherapy (Neumeister, Turner, et al., 1998, though see Lam et al., 2000). In addition, bright light exposure (3,000 lux) has been reported to prevent an ATD induced lowering of mood in healthy, mildly seasonal women (aan het Rot, Benkelfat, Boivin, & Young, 2008).

While 5-HT has certainly been implicated, as in non-seasonal depression, it is unlikely that a single neurotransmitter system is solely responsible. In a preclinical model of the effects of light

deprivation on three monoaminergic neuron systems (5-HT, NA and DA) found that animals kept in constant darkness for 6 weeks showed both increased monoamine cell body apoptosis and behavioral changes indicative of a depressed state compared to animals kept on a 12:12 hour light-dark cycle (Gonzalez & Aston-Jones, 2008). While preliminary research has implicated DA as a possible contributor to the efficacy of light therapy, research supporting the interaction between DA and light is limited and to date, largely based on indirect observations.

One of the first reports on seasonal variations of neurotransmitter levels in human brain primarily highlighted winter-summer differences in hypothalamic 5-HT (Carlsson & Svennerholm, 1980), however, the same paper also mentioned a more complex seasonal rhythm in hypothalamic DA. In contrast, NA levels, while displaying a circadian rhythm, did not change (Carlsson & Svennerholm, 1980). A subsequent post-mortem study also found seasonal variations in levels of DA and HVA in the hypothalamus and nucleus accumbens. Interestingly, again, levels of NA and its metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), did not change (Karson, Berman, Kleinman, & Karoum, 1984). It is acknowledged that many environmental factors vary with season; however the authors concluded that length of daylight was likely the most relevant seasonal variable contributing to the seasonal fluctuations in DA and HVA observed here.

In another study of 68 healthy participants who were characterized by high and low sunshine exposure the authors found that DA receptor availability was affected by relative exposure to natural sunshine. Those participants who had high degrees of sunshine exposure had greater DA D_2/D_3 receptor availability relative to low sunshine participants (Tsai et al., 2011).

While DA has been shown to vary with natural seasonal fluctuations and duration of daylight exposure, DA has also indirectly been implicated in response to artificial bright light. In a preliminary study of bright light exposure in patients with Parkinson's disease (in which the nigrostriatal DA system experiences neuron loss and is thus impaired) it was found that daily one-hour exposures to bright light (1000-1500 lux/daily) led to marked improvements in mood, social activity, motor function and, in some cases, a reduction of DA-replacement therapy dosages of 13-100% (Willis & Turner, 2007).

Finally, it should be noted that while there have been conflicting results of light-induced changes in brain catecholamines, these may be at least partially due to the method used, to small sample sizes, to poor control of the sleep-wake cycle and light/dark exposure, and to lack of a repeated measures design. While not conclusive, human and animal literature offer support for further exploration into the interaction between DA and light and their role in the mechanism of action underlying the efficacy of light therapy.

Indirect Effects of Light on Dopamine

In addition to direct light-DA interactions, light exposure can also indirectly moderate DA synthesis through mediators such as melatonin (MLT). MLT is synthesized in the pineal gland during the dark phase of the light/dark cycle and is thought to act as a time-cue for responding to changes in photoperiod, an effect that has been found in both animals and humans (Vanecek, 1998; Zisapel, 2001). Given MLT's role in the regulation of biological rhythms and its sensitivity to photoperiod, MLT was one of the first systems hypothesized in the etiology of SAD, specifically that increased MLT secretion during the dark part of the year is a trigger for SAD.

Two findings in particular offer support for this hypothesis, the first, that prolonged duration of MLT secretion during the fall/winter is observed in patients with SAD (Wehr et al., 2001), and the second, that exposure to bright light suppresses nocturnal MLT secretion in healthy humans (Lewy et al., 1980; M. Terman, J. S. Terman, & Quitkin, 1988). This theory also indirectly implicates DA, as an inverse relationship between DA content and pineal MLT has been demonstrated (Zisapel, 2001). Taken together these findings support an earlier retinal MLT/DA hypothesis of SAD proposed by Oren et al. (1991), which postulates that bright light will stimulate DA production while suppressing MLT secretion in the retina, and that the opposing actions on these systems function to bring about the antidepressant effect of light therapy. While preliminary, these findings offer further support for the role of DA in the development of SAD and suggest an additional mode by which light may act on the DA system.

Primary Hypotheses

Based on the above literature, the following study was designed to test two primary hypotheses. First, that APTD will produce DA-dependent effects on mood and motivation. Second, that there will be effects of APTD that are prevented by concomitant bright light exposure which will reflect a response that could include both DA-dependent and DA-independent components. Anticipated mood changes will be measured by self-reported ratings of positive and negative mood on the Profile of Mood States (POMS) questionnaire. It is expected that some subjective states (e.g. apathy and energy levels) will be more affected than others (e.g. depression and irritability). Finally, it is also hypothesized that APTD will decrease motivation, impairing the ability to sustain responding when working for monetary reward. This effect will be measured

using a computerized progressive ratio (PR) task during which participants will have an opportunity to work for successive units of monetary reward.

(Manuscript) Dopamine and Light: Dissecting Effects on Mood and Motivational States in Women with Sub-Syndromal Seasonal Affective Disorder

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Abstract

Each winter, 5% of Canadians approximately 10% of the population experience clinically relevant alterations in sleep, appetite, energy and mood, a disturbance commonly called seasonal affective disorder (SAD). Some evidence suggests that catecholamines might play a role. In the present study, 32 healthy women with mild symptoms of SAD were tested between November and March. All subjects slept overnight in a light controlled room on two test days. In the morning, half of the subjects awoke to gradual increases of bright light (3,000 lux), half to dim light (10 lux). On one of the test days, conducted in a randomized and counterbalanced fashion, dopamine was reduced using the acute phenylalanine/tyrosine depletion (APTD) method. On the other day, participants ingested a nutritionally balanced control mixture (BAL). Four hours post-ingestion, participants completed the Profile of Mood States, a series of psychobiological challenges, and a progressive ratio breakpoint task during which participants worked for successive units of $5.00. Compared to BAL, APTD lowered mood, energy, and the willingness to work for monetary reward. The mood-lowering effects were only seen after a psychological challenge and were prevented by bright light exposure; the effects on energy and motivation were independent of light. Together, these results indicate that low dopamine transmission could contribute to some of the symptomatology of SAD, and add to the evidence that the neurobiology of mood and motivational states can be dissociated, the latter being more closely related to dopamine.

Introduction

Disturbances to circadian rhythms, clock genes, and environmental light exposure can alter mood and motivational states (Lamont et al., 2007; Mendlewicz, 2009). The best studied of these, bright light therapy, can alleviate low mood in patients with seasonal affective disorder (SAD) (Rosenthal et al., 1984), non-seasonal major depressive disorder (Tuunainen et al., 2004; Lieverse et al., 2011), antepartum depression (Wirz-Justice et al., 2011), eating disorders (Janas-Kozik et al., 2011; Lam et al., 1994; Braun et al., 1999), and premenstrual dysphoric disorder (Parry et al., 1989) as well as those with sub-syndromal winter mood disturbances (Kasper et al., 1989; Partonen & Lönnqvist, 2000; Avery et al., 2001; Kasper et al., 1990; though see Rosenthal et al., 1987).

Despite the evidence of light's effect on mood,, its mechanism of action remains poorly understood. A number of candidates have been implicated, though. Light exposure can affect serotonin (5-HT; Héry et al., 1972), melatonin (MLT; Lewy et al., 1980; Oren, 1991), cortisol (Jung et al., 2010), and catecholamine levels (Nagayama, 1999). Moreover, decreasing 5-HT synthesis with the acute tryptophan depletion (ATD) method can reinstate symptoms in SAD patients during summer remission (see Young & Leyton, 2002 review), as well as in those successfully treated with light therapy (Lam et al., 1996; Neumeister et al., 1997). In the converse experiment, bright light exposure has been reported to protect against ATD induced mood lowering in healthy, mildly seasonal women (aan het Rot et al., 2008). Accumulating evidence, though, suggests that changes in 5-HT transmission are not sufficient to account for all of the effects of light or antidepressant therapy in this population. Although selective serotonin reuptake

inhibitors (SSRI) have become the first-line treatment for many depressive disorders, including SAD, a large proportion of patients (28-55%) fail to fully recover or experience residual symptoms (Nierenberg & DeCecco, 2001; Nierenberg & Wright, 1999). The SAD symptom cluster of lethargy, psychomotor retardation, weight gain, and low motivation in particular, is suggestive of a hypoactive dopamine (DA) system.

Evidence that light directly influences DA transmission remains, at present, limited and largely indirect. For example, recent neuroimaging evidence suggests that in humans DA D_2/D_3 receptor availability may be affected by relative exposure to natural sunshine (Tsai et al., 2011). A preliminary study in patients with Parkinson's disease indicated that daily one-hour exposure to bright light (1000 - 1500 lux/daily) led to marked improvement in mood, social activity, motor function and, in some cases, a reduction of DA replacement therapy dosages of 13 - 100% (Willis & Turner, 2007). Consistent with this, bright light exposure has been reported to increase striatal blood flow in healthy volunteers (Diehl et al., 1994) while catecholamine depletion with alpha-methyl-para-tyrosine reversed the therapeutic efficacy of bright light in patients with SAD (Neumeister et al., 1998). Finally, in a preclinical model, rodents kept in constant darkness showed increased monoamine cell body apoptosis, changes that were associated with behavioral alterations indicative of a depressed state (Gonzalez & Aston-Jones, 2008).

Based on the above observations, the present study aimed to better characterize the role of DA and light on mood and motivational states using the acute phenylalanine/tyrosine depletion (APTD) method (Leyton et al., 2004; McTavish et al., 1999; Montgomery et al., 2003). With the exception of the transmitter targeted, the present study design is very similar to that of aan het

Rot et al., 2008. Healthy mildly seasonal women were tested in bright or dim light conditions following ingestion of amino acid mixtures that either did or did not contain the DA precursors phenylalanine and tyrosine. Two types of effects were hypothesized: a) effects of APTD irrespective of light condition reflecting responses closely related to DA, and b) effects of APTD that would be prevented by bright light reflecting responses that could include both DA-dependent and DA-independent components.

Materials and Methods

Participant Recruitment

This study was approved by the Institutional Review Board of McGill University's Faculty of Medicine, and all participants provided written informed consent. Participants were recruited through local advertising. Those who expressed interest took part in an initial telephone screen. Volunteers who tentatively met entry criteria were assessed face-to-face using the Structured Clinical Interview for DSM-IV, Non-Patient Edition (SCID-NP; First et al., 2002) and asked to complete the Seasonal Pattern Assessment Questionnaire (SPAQ; Rosenthal, Bradt, & Wehr, 1984), the Short Michigan Alcoholism Screening Test (SMAST; Selzer et al., 1975), the Beck Depression Inventory (BDI; Beck et al., 1961) and a self-rated version of the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD-SR; Williams, Link & Rosenthal, 1988). The SPAQ included the Global Seasonality Scale (GSS), which assesses the degree of seasonal change on six dimensions: sleep, appetite, mood, energy, weight, and social activity, each assessed on a scale from 0 to 4. The minimum

GSS score was a 6 out of 24, which indicates at least mild seasonal changes in mood and behavior, and resembles the symptomatology of sub-syndromal SAD (S-SAD).

Exclusion criteria were past or present axis-1 disorders as defined by the DSM-IV-TR, SAD based on the SIGH-SAD-SR, a BDI score of 15 or higher, use of hormonal contraceptives in the previous three months, abnormal sleep patterns, excessive caffeine, tobacco, or alcohol use, any contraindicated medical conditions, or any current medical illness. Medical health was assessed by a physician and included a physical exam, blood and urine analysis, and electrocardiogram.

Study Design

Participants were assigned to one of two light groups based on order of entry into the study. Of the 18 women allocated to the dim light condition, 2 withdrew following the first test day (one stated side effects, and the other reported illicit drug use post-test day). Of the 20 women allocated to the bright light condition, 4 withdrew after the first test day (3 stated side effects, and 1 stated time constraints). Four of these 6 had received the APTD mixture. A total of 32 women completed the study, 16 in each light group.

Participants were randomly assigned to the bright (3,000 lux) or dim light (10 lux) conditions. Test sessions began at each participant's normal wake time with an initial light setting of 10 lux; if the participant was assigned to the Dim group, they remained in this light setting for the full test day. For Bright group participants, light was gradually increased to 3,000 lux in three increments over 15 minutes (10, 180, and 3,000 lux) and then remained at 3,000 lux for the remainder of the test day.

Amino Acid Mixtures

On each test day, participants ingested the phenylalanine / tyrosine deficient (APTD) or nutritionally balanced mixture (BAL). Their formulation was based on the balanced (100 g) mixture used by Young et al (1985), subsequently adapted by Ellenbogen et al (1996) for the lower body weight of women (~16.7% less than men) and then for targeting phenylalanine and tyrosine (Leyton et al., 2000). In the Dim group (n = 16), 9 subjects received the BAL mixture on their first test day and 7 received the APTD mixture. In the Bright group (n = 16), 8 subjects received the BAL mixture on their first day, and 8 received the APTD mixture.

Experimental Procedure

Testing Environment

All test days took place at the Centre for Study and Treatment of Circadian Rhythms (Douglas Mental Health University Institute, Montréal, Québec, Canada). The testing environment, which included a bathroom, bed, sofa, desk, chair and standalone TV/VCR combo, was a windowless isolation suite free from external time cues. The room was temperature-controlled and soundproof, which allowed the tester to control the environment and ensure uniformity between test sessions. An intercom system allowed for contact with the experimenter in the adjacent control room. Light intensity settings were verified with a calibrated light meter (IL1400A, International Light, Newburyport, MA). Light was administered by ceiling-mounted banks of cool-white fluorescent lamps (4100 K, F32T8/TL841, Philips Lighting, Somerset, NJ, and F032/841, Sylvania, Danvers, MA) covered with filters emitting less than 1% of radiant energy up to 400 nm (Uvalite Plus, KSH, St. Louis, MO). As a result, light of lower wavelengths

(including UV light; 100 - 400 nm), which could cause ophthalmologic and dermatologic problems, was removed.

Pre-Experimental Session Protocol

Participants were asked to keep a regular sleep/wake cycle for at least one week prior to each test day. Test days took place during the follicular phase of the menstrual cycle and at least three days apart. The day prior to each test day participants were asked to consume a low-protein diet (22.6 g of protein; 2,212 kcal), which began at breakfast and ended at midnight.

Participants arrived at the laboratory on the evening before each test day, at least one hour before their normal sleep time. Upon arrival participants handed in all personal devices that indicated the time, were placed in their isolation suite, asked to complete a set of baseline questionnaires, and were screened for recent illicit drug use (Triage Panel for Drugs of Abuse, Biosite Diagnostics) and pregnancy. Lights were turned off at their habitual bedtime and participants slept in total darkness for their individual standard duration of sleep (7 - 9 hours).

Experimental Session

Test days began at each participant's normal wake time based on the schedule maintained the prior week. Subjects were given 30 minutes to get ready for the day after which they completed morning questionnaires, had their vital signs recorded, and a blood sample was taken. Participants were then given one of the amino acid mixtures and asked to consume it as quickly as possible. Subjective rating questionnaires were completed 4, 5, 6, 6.5, and 7 hours post-ingestion of the AA mixture. Between 4 and 6 hours post-ingestion two computer tasks were administered, a challenging facial recognition task and a progressive ratio breakpoint (PR) task

(data from the first task are not presented here). Following completion of the computer tasks participants had a second blood sample taken. At 6.5 hours post-ingestion participants underwent a Negative Mood Induction procedure, as outlined below. Approximately 7 hours after being awoken participants, completed a final set of questionnaires, were given a meal, had their vital signs reassessed, and were sent home (see Figure 3).

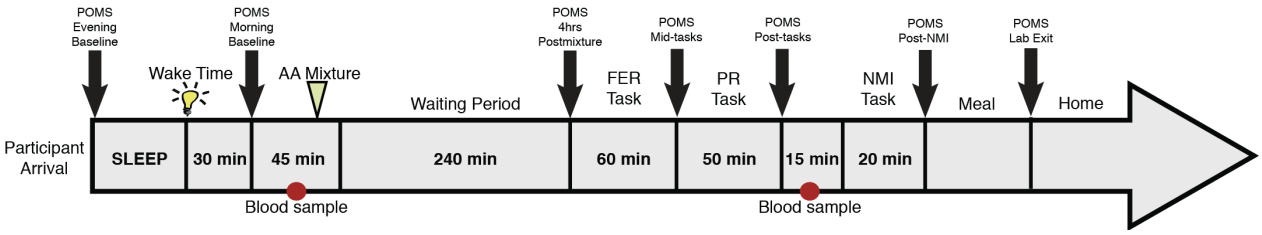

Figure 3: Timeline of the experimental test sessions

Negative Mood Induction Procedure

During the initial screening, subjects were asked to provide and rank 5-10 sad autobiographical memories. On the test day, participants listened to music known to induce a sad mood, including music from Prokofiev's *Alexander Nevsky: Russia under the Mongolian Yoke Russia under the Mongolian Yoke*, Albinoni's *Adagio in G Minor*, Barber's *Adagio pour Cordes*, Grieg's *Peer Gynt: The Death of the Ase*, and Sibelius' *Violin Concerto: Second Movement*. While the music was playing, the researcher narrated a standardized script instructing the participant to listen to the music and recall the personal memory they had ranked as most sad. After reading the script the participant was left alone for 20 minutes with the music playing (Hernandez et al., 2003).

Test Measures

Self-Reported Mood Ratings

Self-reported mood states were measured with the 72-item Profile of Mood States (POMS), a questionnaire sensitive to transient fluctuations in sub-clinical mood states (Lorr et al., 1982). The POMS assesses six bipolar scales (*Composed-Anxious*, *Agreeable-Hostile*, *Elated-Depressed*, *Confident-Unsure*, *Energetic-Tired*, and *Clearheaded-Confused*). Raw POMS scores were normalized to t-scores.

Incentive Motivation

A progressive ratio (PR) breakpoint task was administered to measure motivation to work for monetary reward. The PR task was completed while the participant was seated at a desk with a computer and keyboard. Participants were offered the opportunity to work for $5.00 amounts by repeatedly pressing the letters ‘D’ and ‘R’; each successful D-R combination counted as one press. Participants were told that they may stop at any time, or when the time limit, unknown to them, was up. To receive the first $5.00 required 100 D-R presses. Each subsequent breakpoint increased by a factor of 2.3 (chosen for providing less predictable increases). Participants could complete up to a maximum of 10 reward units. A session ended when the ratio was too large to maintain responding or when the time ran out (50 minutes).

Side-Effects

Dizziness, headache, and nausea have been reported following amino acid mixture ingestion or exposure to bright light (aan het Rot et al., 2008). These three items were assessed using visual analog scales (VAS) with a range from 0 - 100.

Plasma Amino Acid Analysis

Blood samples were collected 15 minutes prior to and approximately 6 hours post-ingestion of the amino acid mixture (5 / 64 not obtained). Blood samples were centrifuged immediately (10 min, 1500 g, 0 ºC) and stored at -80 ºC until further analysis. Plasma amino acid levels were measured using high-pressure liquid chromatography with fluorometric detection (HPLC-FD) on an Ultraspher ODS reverse-phase column (Beckman Coulter, Fullerton, CA) with ophtalaldehyde pre-column derivatization and aminoadipic acid as an internal standard. Total and free tryptophan levels were measured by HPLC-FD on a Bondpak® reverse-phase column (Phenomenex, Torrance, CA).

Statistical analysis

All analyses were performed using IBM SPSS® Statistics Version 19 for Macintosh. Between groups demographic variables were analyzed using independent sample t-tests. Effects of Light and AA Mixture on each test day were analyzed using general linear models. A third independent factor, Time, included the evening lab entry baseline measure and six time points during the test session. To rule out the potential influence of baseline differences on subjective mood ratings on the POMS, or side-effect ratings on the VAS, delta scores were calculated from evening baseline. Each model considered the main effects of Light, AA Mixture and Time, as well as their interaction. Results were deemed significant if p-values were equal to or less than 0.05. Significant interactions were analyzed post-hoc using pair-wise comparisons. All variables were screened for normality using Shapiro-Wilks test, and equality of variance was assessed using Levene's test. These analyses indicated that the PR task breaking point required a Log_{10} transformation to satisfy the assumption of normality required for parametric analyses.

Results

Participants

Average participant age was 23.0 years (SD 4.8), BDI score was 3.13 (SD 3.44), and GSS score was 10.75 (SD 2.73). Participants in the two light conditions were similar on demographic and psychosocial variables with the exception of alcohol consumption per week, which showed a significant group difference (Table 2); however, all drinking histories were below clinically relevant levels and individual differences in alcohol use did not correlate with any of the behavioral variables analyzed.

	Dim (n=16)	**Bright (n=16)**
Age in years, mean (SD)	21.9 (2.6)	24.2 (6.1)
Body Mass Index (kg/m^2), mean (SD)	23.1 (2.3)	22.3 (2.7)
Current alcohol use (drinks/week), mean (SD)	5.1 (2.7)*	2 (2.0)*
Global Seasonality Score at Lab screening, mean (SD)	10.4 (2.2)	11.1 (3.2)
Occupation, % student	50	68.8
Average self-reported normal sleep time (hh:mm), mean (SD h:m)	23:32 (0:54)	00:00 (0:42)
Average self-reported normal wake time (hh:mm), mean (SD h:m)	8:10 (1:21)	8:32 (0:35)

*t_{30}=3.75, p=0.001

Table 2: Subject characteristics

Plasma Amino Acids

On the APTD test session, plasma concentrations of tyrosine and phenylalanine decreased significantly, as reflected by significant AA Mixture x Time interactions (tyrosine $F_{1,26}$ = 151.25,

$p < 0.0001$; phenylalanine $F_{1,26} = 79.56$, $p < 0.0001$). Four hours after ingestion of the AA mixture, the APTD mixture decreased tyrosine and phenylalanine levels by 74.09% and 67.46% from baseline, respectively. In comparison, the BAL mixture increased plasma tyrosine and phenylalanine by 147.11% and 27.01%, respectively. Ingestion of the APTD mixture also significantly decreased the ratio of plasma tyrosine to other LNAA (phenylalanine, tryptophan, leucine, isoleucine, valine, and methionine) by 88.77%, $p < 0.0001$, whereas the BAL mixture did not change the ratio significantly (change of 15.18%, $p = 0.06$). As highlighted by a significant AA Mixture x Time interaction ($F_{1,26} = 155.30$ $p < 0.0001$), ingestion of both AA mixtures significantly decreased the ratio of plasma phenylalanine to other LNAA, but the reductions were more pronounced following APTD compared to BAL with a decrease of 85.34% versus 45.90%, respectively ($p < 0.001$; Table 3).

Amino acid	BAL (a.m.)	BAL (a.m.)	% Difference	APTD (a.m.)	APTD (p.m.)	% Difference
Tyrosine	49.82 (1.59)	123.11 (9.68)**	147.11	52.50 (1.50)	13.60 (0.64)**	-74.09
Phenylalanine	44.79 (1.02)	56.89 (4.27)**	27.01	45.35 (1.07)	14.75 (1.18)**	-67.46
Tyrosine:LNAA	0.131 (0.004)	0.151 (0.011)	15.18	0.135 (0.003)	0.015 (0.001)**	-88.77
Phenylalanine:LNAA	0.116 (0.002)	0.063 (0.003)**	-45.9	0.115 (0.002)	0.017 (0.002)**	-85.34

Table 3: Plasma Levels of Tyrosine and Phenylalanine, and Ratios of Tyrosine and Phenylalanine to Large Neutral Amino Acids at a.m. Baseline and 4 hours Following Amino Acid Ingestion. Biochemical data are presented as mean μmol/l (SD). *$p < 0.001$. **$p < 0.0001$.

Effects of APTD: Not Prevented by Light

Energy

There was a significant AA Mixture x Time interaction for the POMS subscale *Energetic-Tired* ($F_{5,150} = 5.090$, $p = 0.0002$). Compared to the BAL test session, participants' rating scores on the APTD session were decreased during and immediately following completion of the psychosocial tasks with $p = 0.096$ and $p = 0.036$, respectively (Figure 4).

Motivation

A significant main effect of AA Mixture was found for the PR breaking point ($F_{1,30} = 6.624$, $p = 0.015$). On the APTD test session, the breakpoint was significantly lower compared to the BAL test session, and this effect was independent of Light (Figure 5).

Effects of APTD: Prevented by Light

Agreeable-Hostile

There was a significant three-way AA Mixture x Light x Time interaction for the POMS *Agreeable-Hostile* subscale ($F_{5,150} = 2.401$ $p = 0.040$). Participants in the Dim group reported significantly lower scores (i.e., greater hostility) following administration of the APTD mixture compared to BAL (Figure 6). The decrease in *Agreeable-Hostile* scores was significant at Mid-Tasks ($p = 0.012$), Post-Tasks ($p = 0.002$) and Lab Exit ($p = 0.042$). This effect of APTD was not seen in the Bright group at any time point during the day ($p > 0.145$). Visual inspection of the data also indicated a small decrease in *Agreeable-Hostile* scores for subjects in the Bright group

that was not predicated *a priori.* However, there was no significant main effect of Light, and the more prominent difference in scores was between AA Mixtures within the Dim condition.

Elated-Depressed

There was no significant AA Mixture x Light x Time interaction for the POMS *Elated-Depressed* subscale ($F_{5,150} = 1.392$, $p = 0.230$); however, visual inspection of the data revealed that, following completion of the psychosocial tasks, there was a trend for participants in the Dim group to report lower *Elated-Depressed* scores on the APTD day, compared to BAL (Post-Tasks, $p = 0.054$), an effect not seen in subjects tested in the Bright light ($p = 0.597$; Figure 7).

Non-significant POMS Subscales

Other than a main effect of Time ($F_{5,150} > 5.15$, $p < 0.001$), there were no significant main effects or interactions for the three remaining subscales of the POMS: *Composed-Anxious* ($F_{5,150} < 2.332$, $p > 0.137$), *Confident-Unsure* ($F_{5,150} < 2.071$, $p > 0.072$), or *Clearheaded-Confused* ($F_{5,150} < 2.077$, $p > 0.158$).

Side Effects

There was a significant AA Mixture x Time interaction for ratings on the *Nausea* ($F_{5,150} = 2.642$, $p = 0.025$) and *Headache* ($F_{5,150} = 2.731$, $p = 0.022$) subscales of the VAS. Participants' ratings of *Nausea* were significantly higher following APTD at time points 4 (Post-Tasks) and time point 5 (Post-NMI) compared to BAL ($p = 0.010$ and $p = 0.003$, respectively).

There was also a significant AA Mixture x Time interaction for subjective ratings of *Headache*. Post-hoc comparisons showed no significant difference between AA Mixtures at any time point ($p > 0.124$), although the general trend was for ratings of *Headache* to increase over the course of the day with higher reports following APTD compared to BAL.

There was also a significant main effect of Time on the VAS subscale *Dizzy* ($F_{5,150} = 9.087$, $p < 0.0001$). Participant ratings of *Dizzy* increased over the course of the test days with a peak at time point Mid-Tasks and Post-Tasks.

To investigate the role of side-effects on subjective mood scores Pearson's correlations were run with *Nausea* and *Headache*, and *Energetic-Tired*, *Agreeable-Hostile,* and *Elated-Depressed* scores. The variable *Dizzy* was not investigated, as there was only a significant effect of Time, with no effect of AA Mixture or Light condition.

As no significant effect of Light was found for the variable *Energetic-Tired*, correlations were not analyzed separately by light condition. No significant correlations were found between either *Nausea* or *Headache and Energetic-Tired scores* at either time point Mid-Tasks or Post-Tasks ($p > 0.300$ and $p > 0.720$, respectively). Similarly, for *Agreeable-Hostile*, there were no significant associations, for either light condition, at any of the significant time points (Mid-Tasks and Post-Tasks) when correlations were run for *Nausea*, and *Headache* ($p > 0.391$ and $p > 0.620$; respectively). Nor were there any significant correlations between *Elated-Depressed* and *Nausea* or *Headache* ($p > 0.216$ and $p > 0.376$). Finally, no significant correlations were found between PR breakpoint and *Nausea* or *Headache* (*Nausea*: $p > 0.831$; *Headache*: $p > 0.332$).

Negative Mood Induction Procedure

The negative mood induction procedure (NMI) was intended to act as a final stressor; however, the effects were potent, overwhelming any potential modest effects of APTD. For all subscales of the POMS there was a significant effect of Time ($F_{5,150} > 9.375$, $p < 0.001$), which revealed that mood ratings following the NMI (Post-NMI) were significantly lower than all other time points during the test session ($p < 0.027$).

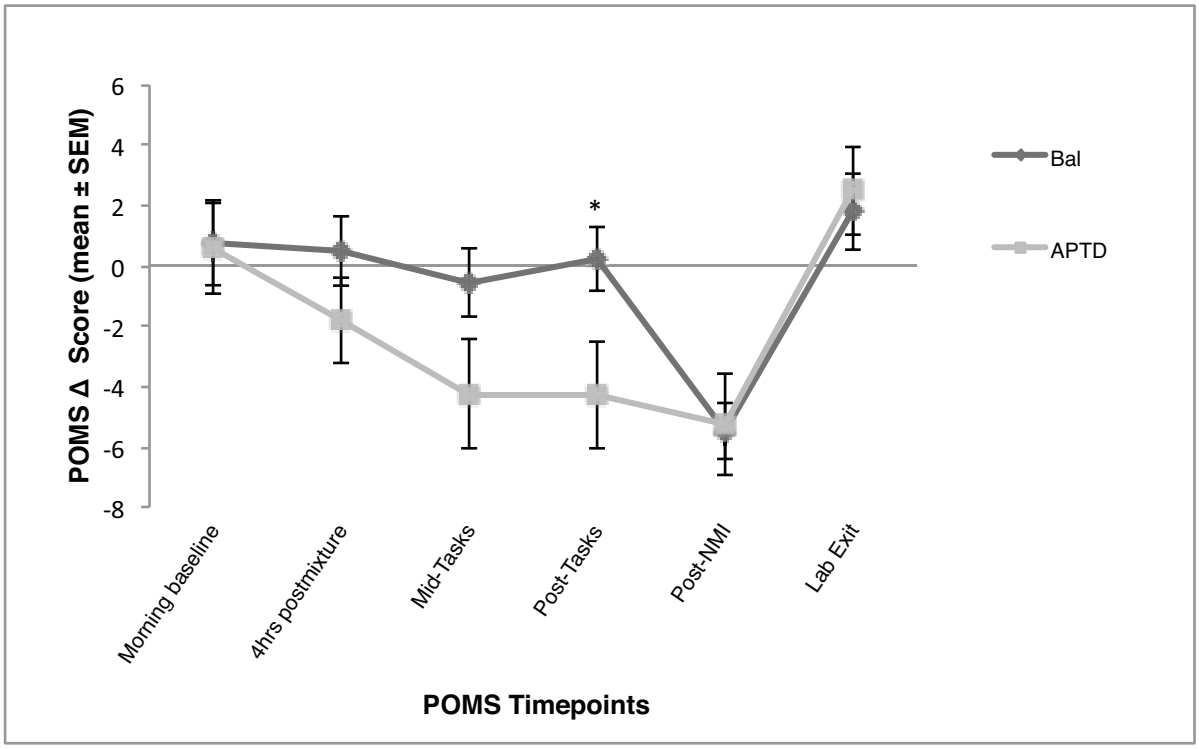

Figure 4: POMS Energetic-Tired subscale delta scores relative to evening baseline for each AA Mixture. Values are shown as mean delta score ± SEM. *$p < 0.05$. Abbreviations: BAL, Balanced amino acid mixture; APTD, Acute Phenylalanine Tyrosine Depletion mixture. Results: There was a significant main effect of AA Mixture with participants reporting significantly lower energy levels Post-Tasks on the APTD day compared to BAL.

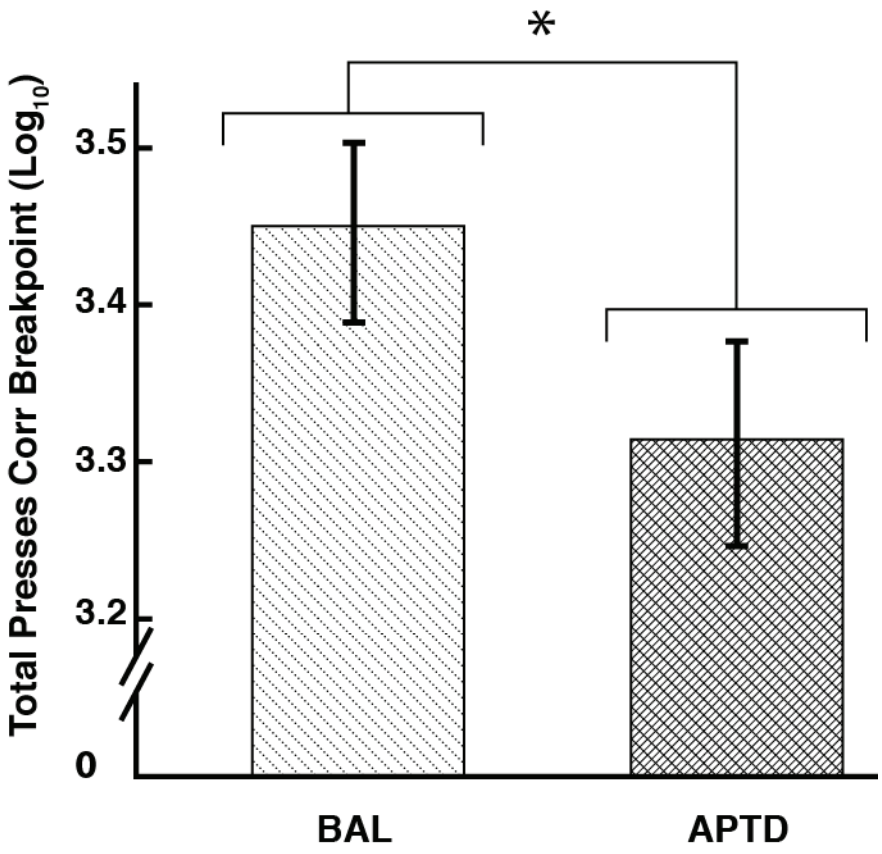

Figure 5: Effect of Acute Phenylalanine Tyrosine Depletion (APTD) on progressive ratio total presses corresponding to the final breakpoint. BAL refers to the control/balanced amino acid mixture, APTD refers to the Acute Phenylalanine Tyrosine Depletion mixture. All participants, regardless of light condition, worked for more $5.00 units on the BAL test day compared to APTD. *$p < 0.05$.

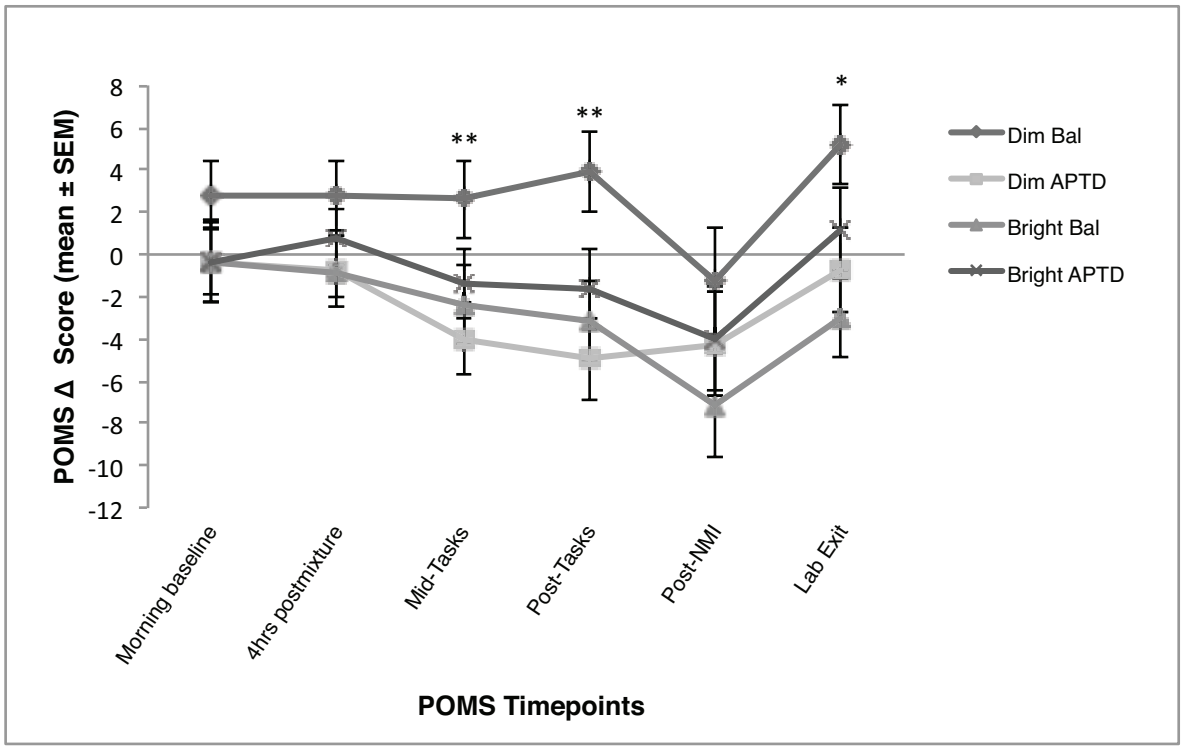

Figure 6: POMS Agreeable-Hostile subscale delta scores per Light group and AA Mixture. Values are shown as mean delta score ± SEM. * $p < 0.05$; ** $p < 0.01$. Abbreviations: POMS, Profile of Mood States, BAL, refers to the control/balanced amino acid mixture; APTD, Acute Phenylalanine Tyrosine Depletion. The Dim group had significantly lower ratings of agreeableness following the APTD test session compared to BAL at Mid-Tasks, Post-Tasks, and Lab Exit.

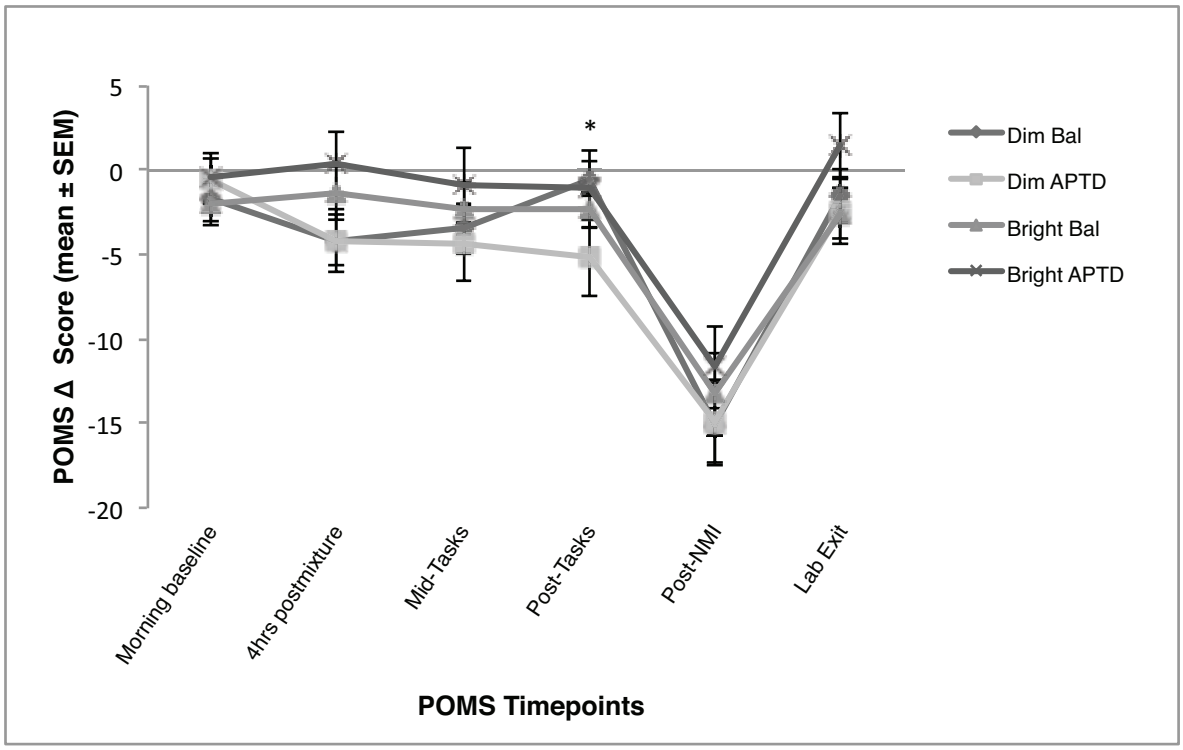

Figure 7: POMS Elated-Depressed subscale delta scores per Light group and AA Mixture. Values are shown as mean delta score ± SEM. * $p < 0.05$. Abbreviations: POMS, Profile of Mood States, BAL, refers to the control/balanced amino acid mixture; APTD, Acute Phenylalanine Tyrosine Depletion. The Dim group showed a trend towards increased ratings of depressed mood at Post-Tasks on the APTD test day compared to BAL.

Discussion

The present study benefited from testing subjects under carefully controlled conditions. Participants arrived the night before, slept in the laboratory and remained there throughout testing procedures without external influences or contact with individuals other than the researcher and nurse. Two main findings emerged. (1) The study provides the first evidence in humans that lowered DA transmission can reduce the motivation to work for a non-pharmacological reward, an effect produced irrespective of light condition. (2) APTD increased susceptibility to low mood following a psychological challenge, an effect that was prevented by bright light exposure. Since APTD alone did not alter mood, and since bright light exposure prevented only some of the effects of APTD, the results support the suggestion that the effects of DA on mood and motivational states are dissociable. More specifically, the results add to the evidence that the effects of DA on motivational states do not require changes in mood (Berridge & Robinson, 1998; Leyton, 2009). They also raise the possibility that bright light exposure combats low mood through non-DA related processes. These results do not negate the possibility that mood and motivational states can influence each other (Lazarus, 1991; Rolls, 2005); indeed, negative mood states can decrease motivation, and susceptibility to low mood could be increased by a combination of low DA-related changes in motivational states and energy levels. The present study though, suggests that mood and motivation are dissociable effects and that rapid changes in affective states may require an additional non-DA related process.

We have reported previously that APTD can induce a mild mood lowering effect specifically when subjects are psychologically stressed (Leyton et al., 2000). The present study replicates this observation and raises the possibility that studies where this mood lowering effect was absent

(e.g., Harrison et al., 2002) could reflect differential lighting conditions. Notably, bright light exposure can alter activity in multiple transmitter systems including 5-HT (Héry et al., 1972; Glass et al., 1995; Penev et al., 1997; Moyer & Kennaway, 2000), and, in a previous study conducted in our lab, mood-lowering effects produced by ATD were consistently prevented by bright light (aan het Rot et al., 2008). Together with the present findings, these studies suggest that DA and 5-HT can independently influence symptoms associated with clinical depression, including SAD.

In previous studies, APTD has been seen to reduce the willingness to work for pharmacological rewards (Barrett et al., 2008; Venugopalan et al., 2011). The present study indicates that lowered DA can also reduce the motivation to work for a non-pharmacological reward. The measure of motivation was the PR breakpoint task. Reductions in breakpoints could occur for multiple reasons, including increased fatigue, lowered mood, or decrease in the ability of the reward to sustain focused interest independent of mood (Berridge & Robinson, 1998; Salamone et al., 2009; Leyton, 2009). Notably, no significant correlations between changes in POMS *Energetic-Tired* scores for both light conditions and PR results were found ($r < 0.218$, $p > 0.147$). These observations suggest that motivation to obtain reward and subjective experience of energy are both DA-related but may be independent effects. This finding is supported by a growing body of animal and human research demonstrating that locomotor activation or fatigue can be behaviorally and anatomically dissociated from motivation to work for or seek out reward (Aberman et al., 1998; Leyton et al., 2007; Salamone et al., 2007; Sellings & Clarke, 2003).

Results from the present study should be interpreted in light of the following considerations. First, as with most studies on light therapy, it is difficult to "blind" the condition of light, which raises the possibility that participants in different light conditions had different expectations with regards to their mood. However, the influence of light condition was only seen in combination with AA Mixture, which was administered in a double-blind fashion, and no independent effects of light were observed. Second, bright light exposure did not prevent the effects of APTD on energy levels or motivation to work for monetary reward despite the fact that SAD summer remission is associated with marked increases in energy and goal-directed behaviors, sometimes to the point of developing hypomanic like states (Rosenthal et al., 1984). This noted, our study investigated the effects of an acute (one day) change in light intensity only. More prolonged changes in light exposure lasting days and weeks might influence DA and DA-related behaviors more potently. In the present study, though, the ability to dissociate effects of APTD and light indicates that it was possible to isolate independent processes. Third, the APTD mixture also increased participants reporting of nausea and headache, which could have affected their mood ratings. However, the mood effects observed were not seen in both light conditions and therefore not believed to be a general product of APTD depletion. Moreover, analysis of the relationship between side-effect variables and mood ratings at the significant time points (Mid- and Post-Tasks) produced no significant correlations. Fourth, the ability of bright light to prevent APTD-induced mood lowering effects but not the decreases in energy levels and motivation to seek monetary reward could reflect either a non-DAergic positive mood promoting mechanism or effects in two separate DA pathways, one light sensitive, the other not. However, just as selective increases in DA transmission do not seem to elevate mood (*e.g.,* see Liggins et al., 2011), APTD alone did not lower mood. Moreover, accumulating evidence suggests that the mechanisms

regulating mood and motivational states are separable (Berridge & Robinson, 1998; Salamone et al., 2009; Leyton, 2009; Treadway & Zald, 2011). Finally, only women were tested. Future studies will need to be conducted in men to determine whether the present effects can be generalized or are gender-specific.

In conclusion, the primary finding in this study was that the neurobiology of energy and motivation can be dissociated from that of mood; the former two effects being DA-dependent, while the latter is likely augmented by DA but involving other systems. Secondly, the interaction effects observed between bright light exposure, DA, and mood suggest that DA and possibly interacting systems (e.g. 5-HT) are sensitive to light and this may have implications for the mechanism of action underlying bright light therapy. In particular, this study highlights the complexity of the monoamine system and supports further investigations of the neurobiological mechanisms of bright light.

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General Discussion

In the present study we used APTD and bright light exposure to investigate the effects of reduced DA synthesis on mood and motivation and the extent that concomitant bright light would be able to attenuate these effects. Our findings support the hypothesis that lowered DA transmission can lead to lowered mood and motivational states resembling those seen in patients with SAD. Intriguingly, though, bright light exposure prevented the effects on mood but not energy levels or the motivation to work for a reward. This dissociation has at least two implications. First, it suggests that the effects of DA on motivational states are not secondary to lowered mood levels. Second, acute light exposure can diminish low DA related mood states, but is likely through a non-DA related processes.

APTD/ DA-Dependent Effects

Motivation

Consistent with previous reports, a DA-dependent reduction in motivation to work for reward was observed. In previous studies, APTD decreased the willingness to work for abused substances on a PR schedule (Barrett et al., 2008; Venugopalan et al., 2011). The present study provides the first evidence in humans that lowered DA can reduce the motivation to work for a non-pharmacological reward.

Motivation to earn monetary reward was measured as Total Presses and Final Breakpoint on a PR schedule. This reduction could be due to a number of factors such as APTD-induced fatigue or saliency of the reward; however, this alternative interpretation is not likely. While monetary

reward does not necessarily produce the same pleasurable or euphoric effects as substances of abuse, it is nonetheless a salient reward, particularly if participants are required to actively engage to receive it (Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004). The observed reduction of PR presses could also be due to decreased energy, particularly in light of the observed decrease in subjective ratings of energy following APTD. However, when correlations were run for *Energetic-Tired* scores and PR results, no significant correlations were found ($r > 0.218$, $p>0.147$).

Although both the animal and human literatures support the conclusion that motor capacity and the willingness to expend effort to obtain a reward are DA-related (Carlsson et al., 1957; Aberman, Ward, & Salamone, 1998; Salamone, Correa, Farrar, & Mingote, 2007), there is also evidence that certain aspects of these processes are separable. For example, in laboratory rodents, exploratory behavior and conditioned place preferences are mediated by different sub-regions of the DA innervated striatum (Sellings & Clarke 2003). In humans, APTD has been shown to selectively decrease responding to reward-paired cues, without producing an overarching motor deficit (Leyton et al., 2007).

Energy

Clinical studies suggests that the most common residual symptoms following treatment with traditional antidepressants (5-HT/NE-targeted) typically include loss of interest, fatigue, loss of energy, and decreased motivation (Nutt et al., 2007); those symptoms associated with decreased DA function and in accordance with the results presented here.

APTD and Light Interactions

An increase in self-reported irritability and depressed mood following APTD was observed, albeit to a lesser extent than the effect on energy and motivation. As anticipated, these mood-lowering effects were prevented by exposure to bright light. The effects resulting from the interaction between light and APTD are evidently distinct from those produced by APTD alone, and are likely attributable to a combination of DA and other neurotransmitter systems. This would also support the finding that a similar (but more significant) mood lowering effect following ATD was seen and that this mood lowering could also be prevented by bright light exposure (aan het Rot et al., 2008), suggesting that the effects on depressed and irritable mood may involve 5-HT and DA systems.

The literature does support at least a contributory role of DA in the regulation of depressed mood and irritability. For example, decreased DA function following cessation of stimulant drugs has been shown to produce a symptom profile consistent with decreased DA function (e.g. fatigue and psychomotor retardation), as well as frequent reports of anhedonia and irritability (Cantwell & McBride, 1998; Newton, Kalechstein, Duran, Vansluis, & Ling, 2004). Moreover, imaging studies have demonstrated an inverse relationship between irritability and [^{18}F]fluorodopa uptake in the caudate (Laakso et al., 2003) as well as putamen DA D_2 receptor density (Farde, Gustavsson, & E. Jönsson, 1997). However, the exact nature of DA in the regulation of mood states remains equivocal. In the 1970s, a series of studies reported that antipsychotic medications (which act primarily by blocking D_2 receptors) decreased subjective ratings of "high" following administration of *d*-amphetamine to stimulant drug abusers (Gunne, Anggård, & L. E. Jönsson, 1972; L. E. Jönsson, 1972; L. E. Jönsson, Anggård, & Gunne, 1971). However, since then, the

majority of studies have failed to replicate this finding (Brauer & de Wit, 1996, 1997; Romach, Glue, & Kampman, 1999).

In accordance with previous studies (Leyton et al., 2000), APTD alone showed no significant mood lowering effects; however, when combined with psychologically stressful tasks, a transient lowering of agreeable and happiness scores was found. Moreover, in the converse studies, subjects who were provided with a tyrosine load experienced diminished changes in the same POMS subscales (hostility, happiness, and energy) following an environmental stressor (cold and hypoxia; Banderet & Lieberman, 1989).

While irritability and mood can be augmented by DA, the lack of a consistent or robust effect in the literature suggests that there are likely other light sensitive systems involved; e.g., 5-HT, and/or NA. Research into mood and aggression highly implicate 5-HT as a significant contributor to these effects, and in the previously mentioned ATD study, a more general and substantial mood lowering (including depression and irritability) was seen. Reviews of ATD studies have also reported that the most common effects are mild mood lowering and increased irritability (Booij, Van der Does, & Riedel, 2003; Ruhé, Mason, & Schene, 2007; Young & Leyton, 2002). The mood lowering following APTD and ATD are not likely exclusive effects, as monoamine systems are known to interact. Moreover, light is known to exert some regulator effects in of these systems. However, it is difficult to know with certainty whether the bright light is acting directly on DA and/or 5-HT to produce the observed effect, or, if other neurotransmitter systems are involved. Nonetheless, the finding that bright light prevented an APTD lowering of mood here, as well as in the ATD study supports the hypothesis that the action of light therapy is likely

mediating both serotonergic and catecholaminergic systems or restoring the functional interactions between them (Neumeister et al., 2001). This hypothesis was initially postulated from studies showing that both serotonergic (ATD) and catecholaminergic (DA/NA) depletions reversed the effects of light therapy (Neumeister et al., 1998). Our findings, as well as those of aan het Rot et al., (2008), go further to demonstrate that bright light can prevent the mood lowering effects of monoamine depletions.

In animals, it has been shown that there are connections between the 5-HT and catecholamine systems (Guiard et al., 2008; Kaehler et al.,1999). Animal studies also demonstrate that light exposure can have anatomic and behavioral effects on these systems. One study in particular looked that at the NA, 5-HT, and DA systems (in the LC, SCN and VTA, respectively) and found that animals kept in constant darkness had increased cell body apoptosis in all three systems and, this damage was associated with the development of depressive-like symptoms (Gonzalez & Aston-Jones, 2008). It has also been shown that in the rat dorsal raphe, under basal conditions, the number of spontaneously active 5-HT neurons and their firing rate are significantly lower when measured during the dark phase of the light/dark cycle (Domínguez-López et al., 2011). Moreover, during the light phase, administration of low-dose MLT decreased 5-HT firing, suggesting another possible mechanism (Light – MLT – 5-HT), by which light may mediate brain monoamine systems. The functional interactions between brain monoamine systems and the moderating effect of bright light on these systems deserves further study and the mood modulating effects of light on the interacting monoamine systems in humans also needs to be further investigated.

Independent Light Effects

No effects of bright light exposure alone were found. This was initially surprising given the literature that individuals with S-SAD respond well to bright light therapy, but is consistent with the similar ATD study which also reported no effect of bright light exposure alone (aan het Rot et al., 2008). This finding is attributed to the relatively healthy and mildly seasonal population tested here. Early studies of SAD and S-SAD patients that reported an efficacious response to bright light exposure very often reported co-morbid psychiatric conditions and higher seasonality scores than were seen in the present study. In this respect, our mildly seasonal participants are more representative of healthy controls, a population that has shown no significant mood response to short-term light therapy (Kasper et al., 1988, 1989). This is also consistent with the previously mentioned ATD study, which showed that the effects of ATD on ratings of confusion and depression were only seen in those subjects with a GSS score above the sample mean, whereas no effect was seen in participants with lower GSS scores. Conversely, there have been studies which report that individuals with low GSS scores (2-6) have a beneficial response to light therapy and that this response is not different from individuals with higher GSS scores (7-16; Norden & Avery, 1993).

Another consideration relevant to the interpretation of this result is that a beneficial response to light therapy typically occurs within two to four days, with measurable improvement in affect seen after approximately one week (Lam & Levitt, 1999). Therefore, it is unlikely that any measurable change of subjective mood ratings, in response to bright light alone, would have been observed with such a limited exposure time (~8 hours), particularly in subjects reporting only mild seasonal disturbances.

Strengths and Limitations

The results of the present study should be interpreted in light of the following considerations. First, one methodological shortcoming of studies testing the effects of bright light is the lack of an adequate control condition, as it is very difficult "blind" the condition of light. In the present study, as with all studies comparing bright and dim light condition, participant expectations that bright light may have positive mood effects should be considered. One option would be to test each participant on four occasions and under both light conditions. This design would decrease variability between light conditions and eliminate expectation effects. However, it would introduce other confounds, including marked changes in familiarity with the environment and test challenges, as well as likely increasing drop out rates significantly due to the extensive demands on time. That noted, while participants and researchers could not be blind to the light condition, administration of the amino acid mixtures was done under double-blind conditions. If expectations from the bright light condition were a significant confounding factor then independent effects of light would have observed, which was not the case. Given that the influence of light was only seen in combination with the amino acid mixtures, it seems reasonable to exclude expectation effects as a significant influence.

Second, the test environment is artificial and due to the nature of the study design, it is likely stressful. Spending long hours in relative social isolation while being a test subject could itself have had an effect on mood; however, if this were the case then these effects would have been seen over both test days.

Third, the study was limited to women and, as a result, cannot be generalized across sexes. The study was limited to women for a number of reasons. First, seasonal fluctuations in mood and behavior have a greater prevalence in women, particularly younger women (Magnusson, 2000), and a response to light therapy has been shown in individuals who experience at least S-SAD. Given that the effects of APTD have not been pronounced, and in the hope of seeing an effect of light and/or an interaction with the APTD, the study was limited to women.

Fourth, the APTD method putatively affects the central brain DA system. Studies using PET imaging have shown lowered DA release in response to APTD (Leyton et al., 2004; Montgomery, McTavish, Cowen, & Grasby, 2003). Various studies have also shown consistent decreases in the targeted amino acids compared to plasma concentrations of other LNAA (Sheehan, Tharyan, McTavish, Campling, & Cowen, 1996; Moja, Lucini, & Benedetti, 1996) and increases in circulating levels of prolactin, a neuroendocrine index of decreased DA transmission (Harmer et al., 2001) but not changes to melatonin, an index of noradrenergic function (Sheehan et al., 1996). The efficacy of the APTD method is also well documented in animal studies (Fernstrom & Fernstrom, 1995; McTavish, Cowen, & Sharp, 1999).

Furthermore, there is no direct evidence that APTD decreases catecholamine neurotransmission specifically, and may be acting on other neurotransmitter systems. As mentioned previously, in animal studies there are known anatomical and functional connections between 5-HT and catecholamine systems, suggesting that the effects of APTD could be acting on distal neurotransmitter systems. A recent imaging study in humans showed the first results of lowered 5-HT transmission on DA release, concluding that that ATD decreased limbic DA release, and

augmented a cocaine-induced striatal DA response (Cox et al., 2011). While this was the first study of its kind, it offers support for the idea that monoamine precursor depletions may have secondary effects on interacting transmitters. Nonetheless, the large body of evidence from both animal and human studies supports that the primary effect of APTD is on DA transmission.

The primary advantage of this study is the highly controlled nature of the testing protocol and environment. All test days took place in a tightly regulated environment with no exposure to outside cues except for minimal interaction with a researcher and nurse. In addition, regulation of participants' sleep/wake cycle, diet, and hormone levels (no subjects were taking hormonal contraceptives and all were tested during the follicular phase of their menstrual cycle) afford greater reliability to the results by decreasing the influence of these possible confounding variables. In addition, by requiring participants to sleep in the testing environment the evening before we eliminated the possibility of any confounding influence of light exposure or other variables during transport to the lab on the test day.

Future Directions

It would be of great interest to repeat the current study, using both APTD and ATD, and a combined mixture, with imaging techniques to further dissect the mechanisms contributing to the observed mood and behavioral effects of the amino acid mixtures and light exposure. To do this would have implications for the application of bright light as a therapeutic tool. Given the large number of patients who fail to respond to traditional antidepressant, the development of alternative therapeutic tools is necessary. As highlight in a recent editorial (Young, 2011), while no single therapeutic intervention has proven overly effective for the treatment of depression, a

combination of different therapies, perhaps traditional and non-traditional, may be more successful. However, to determine the combination(s) most effectively will require elucidation of the mechanisms underlying non-traditional therapies such as bright light so that specific symptom presentation may be targeted.

Conclusion

In conclusion, the primary findings are that bright light exposure can prevent APTD's effects on mood but not energy and motivation to seek a reward. These results suggest that (i) phototherapy could be an effective treatment for at least some DA-related symptoms of SAD and other mood disorders, and (ii) DA is closely related to energized appetitive states but more weakly related to frank changes in mood, affective states that require the additional contribution of other processes. Together, these findings highlight the importance of controlling for light conditions during APTD studies, and indicate that the neurobiology of mood and motivation can be dissociated.

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